

## PRODUCT MONOGRAPH

Pr **ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>**

Indacaterol maleate inhalation powder hard capsules

75 mcg indacaterol

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> capsules to be used only with the supplied ONBREZ<sup>®</sup>  
BREEZHALER<sup>®</sup> inhalation device

Long-acting beta<sub>2</sub>-agonist

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Date of Preparation:

**December 5, 2011**

Date of Revision:

**January 2, 2015**

Submission Control No: 178064

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# Pr ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>

Indacaterol maleate

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral Inhalation	inhalation powder hard capsules, 75 mcg	Gelatine (capsule shell), lactose monohydrate

### INDICATIONS AND CLINICAL USE

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> (indacaterol maleate) is a long-acting beta<sub>2</sub>-agonist (LABA) indicated for long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

- ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> is not indicated for the relief of acute deterioration of COPD.
- ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> is not indicated for asthma use. The safety and effectiveness of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> in asthma have not been established.

No dosage adjustment is required for geriatric patients, patients with mild and moderate hepatic impairment, or renally impaired patients. No data are available for subjects with severe hepatic impairment (see CLINICAL PHARMACOLOGY for details).

#### **Pediatrics (less than 18 years of age):**

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should not be used in patients under 18 years of age.

### CONTRAINDICATIONS

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> (indacaterol maleate) is contraindicated in patients with hypersensitivity to indacaterol maleate or to any other component of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>. For a complete listing, see the Dosage Forms, Composition and packaging section of the product monograph.

All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication (see WARNINGS AND PRECAUTIONS). ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> is not indicated for the treatment of asthma.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

#### WARNING: ASTHMA RELATED DEATH

Long-acting beta<sub>2</sub>-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo controlled US study that compared the safety of another LABA (salmeterol) or placebo added to patients' usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including indacaterol maleate, the active ingredient of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>.

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> is only indicated for COPD. The safety and efficacy of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> in patients with asthma have not been established. ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> is not indicated for the treatment of asthma.

#### General

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> is only indicated for COPD. ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should not be used in asthma due to the absence of long-term safety and efficacy data in asthma with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>.

It has been shown that long-acting beta<sub>2</sub>-adrenergic agonists may increase the risk of asthma-related death. Data from a 28-week, large placebo-controlled US study comparing the safety of a twice-daily long-acting beta<sub>2</sub>-adrenergic agonist (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13 out of 13,176 in patients treated with salmeterol vs. 3 out of 13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma related death may represent a class effect of the long-acting beta<sub>2</sub>-adrenergic agonists, including ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>. No study adequate to determine whether the rate of asthma-related death is increased in patients treated with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> has been conducted.

Serious asthma-related events, including death, were reported in clinical studies with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta<sub>2</sub>-adrenergic agonists.

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> is not indicated for the initial treatment of acute episodes of bronchospasm, i.e., as a rescue therapy. ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta<sub>2</sub>-agonist. ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> in this setting is inappropriate.

When prescribing ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>, the healthcare professional should also provide the patient with an inhaled, short-acting bronchodilator for treatment of COPD symptoms that occur acutely, despite regular once-daily use of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>.

When beginning treatment with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>, patients who have been taking inhaled, short-acting bronchodilators on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

As with other inhaled beta<sub>2</sub>-adrenergic drugs, ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should not be used more often or at higher doses than recommended.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta<sub>2</sub>-agonist becomes less effective or the patient needs more inhalation of short-acting beta<sub>2</sub>-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> beyond the recommended dose is not appropriate in this situation.

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should not be used in conjunction with other long-acting beta<sub>2</sub>-adrenergic agonists or medications containing long-acting beta<sub>2</sub>-adrenergic agonists as this may increase the risk of adrenergic stimulation (see DRUG INTERACTIONS).

### **Cardiovascular**

Indacaterol, like other beta<sub>2</sub>-adrenergic agonists, may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic and/or diastolic blood pressure, and/or symptoms. In case such effects occur, the drug may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce ECG changes, such as flattening of the T wave, QTc interval prolongation, and ST segment depression, although the clinical significance of these findings is unknown.

Therefore, ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>, like other beta<sub>2</sub>-adrenergic agonists, should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias and hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta<sub>2</sub>-adrenergic agonists.

Beta<sub>2</sub>-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment (see DRUG INTERACTIONS) which may increase the susceptibility to cardiac arrhythmias.

## **Endocrine and Metabolism**

### **Coexisting Conditions**

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta<sub>2</sub>-agonist salbutamol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

### **Hypokalemia**

Beta<sub>2</sub>-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects (see ACTION AND CLINICAL PHARMACOLOGY). The decrease in serum potassium is usually transient, not requiring supplementation.

### **Hyperglycemia**

Inhalation of high doses of beta<sub>2</sub>-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> plasma glucose should be monitored more closely in diabetic patients.

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> has not been investigated in patients whose diabetes mellitus is not controlled.

## **Respiratory**

### **Paradoxical Bronchospasm**

As with other inhalation therapy, administration of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should be discontinued immediately and alternative therapy instituted.

## **Sensitivity**

### **Immediate Hypersensitivity Reactions**

Immediate hypersensitivity reactions may occur after administration of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should be discontinued immediately and alternative therapy instituted. The patient should NOT be re-challenged with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> (see CONTRAINDICATIONS).

## **Special Populations**

**Pregnant Women:** No clinical data on exposed pregnancies in COPD patients are available. Studies in animals have shown reproductive toxicity associated with an increased incidence of one type of skeletal abnormality in rabbits. The potential risk for humans is unknown. Because

there are no adequate and well-controlled studies in pregnant women, indacaterol should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

**Labour and delivery:** Like other beta<sub>2</sub>-adrenergic agonists, ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> may inhibit labor due to a relaxant effect on uterine smooth muscle.

**Nursing Women:** It is not known whether indacaterol passes into human breast milk. Because many drugs are excreted in human milk, and because indacaterol has been detected in the milk of lactating rats, the use of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

**Pediatrics (less than 18 years of age):** ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should not be used in patients under 18 years of age. The safety and effectiveness of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> in patients under 18 years of age have not been established.

**Geriatrics (over 65 years of age):** No adjustment of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> dosage in geriatric patients is warranted. Of the total number of patients who received ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> in the clinical studies from the pooled 3-month database, 239 were <65 years, 153 were 65–74 years and 57 were ≥75 years of age. No overall differences in effectiveness were observed, and in the 3-month pooled data, the adverse drug reaction profile was similar in the older population compared to the patient population overall.

**Hepatic Impairment:** Patients with mild and moderate hepatic impairment did not show any relevant changes in C<sub>max</sub> or AUC. Furthermore, protein binding did not differ between mild and moderate hepatically impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

**Renal Impairment:** Due to the very low contribution of the urinary pathway to total body elimination, a study in renally impaired subjects was not performed.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

Long-acting beta<sub>2</sub>-adrenergic agonists such as ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> increase the risk of asthma-related death. ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> is not indicated for the treatment of asthma (See BOXED WARNING and WARNING AND PRECAUTIONS).

#### *Summary of safety profile*

The safety experience with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> comprises exposure of up to one year at doses up to 600 mcg once-daily.

The most common adverse drug reactions at the recommended dose of 75 mcg of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> once-daily were cough, nasopharyngitis, headache, nausea and oropharyngeal

pain, muscle spasms and viral upper respiratory tract infection. These were in the vast majority mild or moderate.

### *Description of population*

The ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> safety database reflects a total of 4,764 patients exposed to ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> at doses of 75 mcg once-daily or greater for at least 12 weeks in 11 randomized, double-blind, placebo and active-controlled clinical trials. In these trials, 449 patients were exposed to the recommended dose of 75 mcg for up to 3 months, and 2,611, 1,157 and 547 COPD patients were exposed to a dose of 150, 300 or 600 mcg for one year, respectively. Overall in Phase III, approximately 41% of patients had severe COPD. The mean age of patients was 64 years, with 46% of patients aged 65 years or older, and the majority (80%) was Caucasian.

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Table 1 displays adverse drug reactions observed during a 3-month exposure at the recommended dose of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> 75 mcg once-daily with the corresponding control group. Adverse drug reactions are listed according to MedDRA system organ class in descending order of frequency. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first.

**Table 1**      **Number and frequency of adverse drug reactions (>1.0% and higher than placebo) in COPD patients exposed to ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> for 3 months, in controlled studies**

	<b>Indacaterol 75 mcg once daily n=449 n (%)</b>	<b>Placebo n=445 n (%)</b>
<b>Gastrointestinal disorder</b>		
Nausea	11 (2.4)	4 (0.9)
<b>Infections and infestations</b>		
Viral upper respiratory tract infection	5 (1.1)	3 (0.7)
<b>Musculoskeletal and connective tissue disorders</b>		
Muscle spasms	6 (1.3)	2 (0.4)
<b>Nervous system disorders</b>		
Headache	23 (5.1)	11(2.5)
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough	29 (6.5)	20 (4.5)
Nasopharyngitis	24 (5.3)	12 (2.7)
Oropharyngeal pain	10 (2.2)	3 (0.7)



### **Less-common Clinical Trial Adverse Drug Reactions (<1%):**

Additional adverse drug reactions reported in <1% (and higher than placebo) were as follows:

- Musculoskeletal and connective tissue disorders: musculoskeletal pain, myalgia
- General disorders and administration site conditions: edema peripheral, chest discomfort
- Cardiac disorders: atrial flutter
- Gastrointestinal disorders: dry mouth
- Respiratory, thoracic and mediastinal disorders: sinus congestion, rhinorrhoea

At higher doses, up to 600 mcg once-daily, the safety profile of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> was overall similar to that of the recommended dose. Additional adverse drug reactions at the higher doses were pneumonia, ischemic heart disease, palpitations, tachycardia, paradoxical bronchospasm, pruritus/rash, sinusitis and tremor. Furthermore, atrial fibrillation, angina pectoris, diabetes mellitus and hyperglycemia, and muscle spasm occurred more frequently at higher doses than at the recommended dose.

### **Cough experienced post-inhalation**

In Phase III clinical studies, health care providers observed during clinic visits on average 14% of patients experienced a sporadic cough that occurred usually within 15 seconds following inhalation of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> and typically lasted for 5 seconds. There is no evidence that cough experienced post inhalation is associated with bronchospasm, exacerbations, deteriorations of disease or loss of efficacy.

### **Postmarket Adverse Drug Reactions**

Post-market adverse reactions such as atrial fibrillation was reported in patients treated with 75 mcg once-daily. Additionally, post-market adverse reactions such as hypersensitivity reactions, paradoxical bronchospasm, tachycardia/heart rate increase/palpitations, pruritus/rash and dizziness have been identified for indacaterol 150 mcg and 300 mcg once-daily. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions**

#### ***Drugs known to prolong QTc interval***

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>, as other beta<sub>2</sub>-adrenergic agonists, should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Drugs known to prolong the QT-interval may increase the risk of ventricular arrhythmia (see WARNINGS AND PRECAUTIONS).

### ***Sympathomimetic agents***

Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> (see WARNINGS AND PRECAUTIONS).

### ***Treatments Leading to Hypokalaemia***

Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta<sub>2</sub>-adrenergic agonists (see WARNINGS AND PRECAUTIONS).

### ***Beta-adrenergic blockers***

Beta-adrenergic blockers may weaken or antagonize the effect of beta<sub>2</sub>-adrenergic agonists. Therefore ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution.

### ***Metabolic and transporter based drug interaction***

Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>. Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin, verapamil and ritonavir). Verapamil was used as the prototypic inhibitor of P-gp and resulted in 1.4- to two-fold increase in AUC and 1.5-fold increase in C<sub>max</sub>. Co-administration of oral erythromycin with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2 fold for C<sub>max</sub>. Combined inhibition of P-gp and CYP3A4 by the very strong dual inhibitor ketoconazole caused a two-fold and 1.4-fold increase in AUC and C<sub>max</sub> of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>, respectively. Concomitant treatment with another dual inhibitor of CYP3A4 and P-gp, ritonavir, resulted in a 1.6-fold to 1.8-fold increase in AUC whereas C<sub>max</sub> was unaffected. No adjustment is warranted for the 75 mcg dose.

**Table 2**      **Established or Potential Drug-Drug Interactions**

<b>Drug</b>	<b>Ref.</b>	<b>Effect</b>	<b>Clinical Comment</b>
Beta-adrenergic blockers (including ophthalmic agents)	T	Potential pharmacodynamic interaction (antagonism of pulmonary effects resulting in severe bronchospasm)	If concomitant therapy is required, consider cautious use of cardioselective β-adrenergic blocking agents
Xanthine derivatives	T	Potential pharmacodynamic interaction (increased risk of hypokalemia)	Cautious use is recommended
Corticosteroids	T	Potential pharmacodynamic interaction (increased risk of hypokalemia)	Cautious use is recommended
Diuretics, non-potassium sparing	T	Potential pharmacodynamic interaction (increased risk of	Cautious use is recommended

		hypokalemia	
MAO inhibitors	T	Potential pharmacodynamic interaction (prolongation of the QT <sub>c</sub> interval and increased risk of ventricular arrhythmias)	Caution is recommended during concomitant therapy
Tricyclic antidepressants	T	Potential pharmacodynamic interaction (prolongation of the QT <sub>c</sub> interval and increased risk of ventricular arrhythmias)	Caution is recommended during concomitant therapy
QT <sub>c</sub> prolonging drugs	T	Potential pharmacodynamic interaction (prolongation of the QT <sub>c</sub> interval and increased risk of ventricular arrhythmias)	Caution is recommended during concomitant therapy
Sympathomimetic agents	T	Potential pharmacodynamic interaction (additive pharmacologic and adverse effects)	Caution recommended for concomitant use of indacaterol and sympathomimetic agents administered by any route
Inhibitors of Cytochrome P450 and P-gp efflux transporter	CT	Potential pharmacokinetic interaction with the inhibitors of CYP3A4 with maximal 2-fold increase in exposure with the potent CYP3A4 inhibitor ketoconazole.	ONBREZ BREEZHALER has been evaluated in clinical studies up to 600 mcg at steady state, with exposure exceeding that observed in combination with ketoconazole, without evidence an impact on safety of therapeutic doses

Legend: C = Case Study; CT = Clinical Trial; CS = Class Statements; T = Theoretical

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

No dosage adjustment is required for geriatric patients, patients with mild and moderate hepatic impairment, or renally impaired patients. No data is available for subjects with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY).

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should not be used in patients under 18 years of age.

### Recommended Dose and Dosage Adjustment

The recommended dosage of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> is the once-daily inhalation of the contents of one 75 mcg capsule using the BREEZHALER<sup>®</sup> inhaler.

### Missed Dose

Patients should be advised that if they forget to take a dose, they should take one as soon as they

remember. ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should not be used more than one time every 24 hours.

### **Administration**

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should be administered around the same time everyday by the oral inhalation route. ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> should always be administered with the ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> inhalation device.

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> capsules must not be swallowed. ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> capsules must always be stored in the blister, and only removed IMMEDIATELY BEFORE USE.

### **OVERDOSAGE**

In COPD patients single doses of 40 times the 75 mcg dose were associated with a moderate increase in pulse rate, systolic blood pressure and QT<sub>c</sub> interval.

An overdose of indacaterol is likely to lead to exaggerated effects typical of beta<sub>2</sub>-adrenergic stimulants *i.e.*, angina, hypertension or hypotension, tachycardia, with rates up to 200 bpm, tremor, palpitations, nervousness, headache, nausea, dry mouth, vomiting, drowsiness, muscle cramps, ventricular arrhythmias, metabolic acidosis, fatigue, malaise, insomnia, hypokalaemia and hyperglycaemia. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>.

Supportive and symptomatic treatment is indicated. In serious cases, patients should be hospitalised. There is insufficient evidence to determine if dialysis is beneficial for overdose of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>. Cardiac monitoring is recommended in cases of overdose. Use of cardioselective beta-blockers may be considered, but only under the supervision of a physician and with extreme caution since the use of beta-adrenergic blockers may provoke bronchospasm.

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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### **ACTION AND CLINICAL PHARMACOLOGY**

#### **Mechanism of Action**

Indacaterol is a long-acting beta<sub>2</sub>-adrenergic agonist for once-daily administration. When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a nearly full agonist at the human beta<sub>2</sub>-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action. The pharmacological effects of beta<sub>2</sub>-adrenoceptor agonists, including indacaterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic monophosphate). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that indacaterol has more than 24-fold greater potency at beta<sub>2</sub>-

receptors compared to beta<sub>1</sub>-receptors and 20-fold greater potency compared to beta<sub>3</sub>-receptors. This selectivity profile is similar to formoterol. The clinical significance of this finding is unknown.

Although beta<sub>2</sub>-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-receptors are the predominant receptors in the human heart, there are also beta<sub>2</sub>-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of beta<sub>2</sub>-adrenergic receptors in the heart is unclear, but their presence raises the possibility that even highly selective beta<sub>2</sub>-adrenergic agonists may have cardiac effects.

## **Pharmacodynamics**

### **Primary Pharmacodynamic Effects**

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> provided consistently significant improvement in lung function (as measured by the forced expiratory volume in one second, FEV<sub>1</sub>) over 24 hours in a number of clinical pharmacodynamic and efficacy trials. There was a rapid onset of action within 5 minutes after inhalation of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> and a peak effect occurring between 2-4 hours following the dose. There was no evidence for tachyphylaxis to the bronchodilator effect after repeated dosing for up to 52 weeks. The bronchodilator effect did not depend on the time of dosing (morning or evening).

### **Secondary Pharmacodynamic Effects**

The characteristic adverse effects of inhaled beta<sub>2</sub>-adrenergic agonists occur as a result of activation of systemic beta-adrenergic receptors. The most common adverse effects include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in serum potassium and increases in plasma glucose.

### **Effects on cardiac electrophysiology**

The effect of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> on the QT interval was evaluated in a double-blind, placebo- and active (moxifloxacin)-controlled study following multiple doses of indacaterol 150 mcg, 300 mcg or 600 mcg once-daily for 2 weeks in 404 healthy volunteers. Fridericia's method for heart rate correction was employed to derive the corrected QT interval (QT<sub>cF</sub>). Maximum mean prolongation of QT<sub>cF</sub> intervals was <5 ms, and the upper limit of the 90% confidence interval was below 10 ms for all time-matched comparisons versus placebo. There was no evidence of a concentration-delta QT<sub>c</sub> relationship in the range of doses evaluated. During this study, there were no clinically significant QT<sub>c</sub> prolongations.

### **Electrocardiographic monitoring in patients with COPD**

The effect of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> on heart rate and rhythm was assessed using continuous 24-hour ECG recording (Holter monitoring) in a subset of 605 patients with COPD from a 26-week, double-blind, placebo-controlled Phase III study (see CLINICAL TRIALS). Holter monitoring occurred once at baseline and up to 3 times during the 26-week treatment period (at weeks 2, 12 and 26).

A comparison of the mean heart rate over 24 hours showed no increase from baseline. Hourly heart rate analysis was similar compared to placebo. The pattern of diurnal variation over 24 hours was maintained and was similar to placebo.

No difference from placebo was seen in the rates of atrial fibrillation, time spent in atrial fibrillation and also the maximum ventricular rate of atrial fibrillation.

No clear patterns in the rates of single ectopic beats, couplets or runs were seen across visits.

Because the summary data on rates of ventricular ectopic beats can be difficult to interpret, specific pro-arrhythmic criteria were analyzed. In this analysis, baseline occurrence of ventricular ectopic beats was compared to change from baseline, setting certain parameters for the change to describe the pro-arrhythmic response. The number of patients with a documented pro-arrhythmic response was very similar compared to placebo.

Overall, there was no clinically relevant difference in the development of arrhythmic events in patients receiving indacaterol treatment over those patients who received placebo.

### **Effects on serum potassium and plasma glucose**

Changes in serum potassium and plasma glucose were evaluated in COPD patients in double-blind, placebo-controlled Phase III studies (see CLINICAL TRIALS). In pooled data, at the recommended dose, at 1 hour post-dose at week 12, there was no change compared to placebo in serum potassium; the change in mean plasma glucose was 0.07 mmol/L.

### **Tachyphylaxis**

Tolerance to the effects of inhaled beta-agonists can occur with regularly-scheduled, chronic use. ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> consistently provided significant improvement in lung function (as measured by the forced expiratory volume in one second, FEV<sub>1</sub>) over 24 hours in a number of clinical pharmacodynamic and efficacy trials. There was no evidence for tachyphylaxis to the bronchodilator effect after repeated dosing for up to 52 weeks.

### **Pharmacokinetics**

**Table 3 Summary of indacaterol's Pharmacokinetic Parameters**

<b>C<sub>max</sub><sup>1</sup></b>	<b>t<sub>1/2</sub> (h)<sup>2</sup></b>	<b>AUC<sub>0-24</sub><sup>1</sup> (pg/mL)</b>	<b>Clearance<sup>3</sup> (L/h)</b>	<b>Volume of distribution<sup>3</sup> (L)</b>
100 (39)	45.5-126	1150 (551)	18.8 -23.3	2360-2560

<sup>1</sup>Arithmetic mean (SD) systemic exposure in COPD patients treated once daily for 14/15 days with 75 mcg indacaterol;

<sup>2</sup>Range of arithmetic mean half-lives observed across clinical trials;

<sup>3</sup>Determined following intra-venous indacaterol administration

**Absorption:** The median time to reach peak serum concentrations of indacaterol was approximately 15 min after single or repeated inhaled doses. Systemic exposure to indacaterol increased with increasing dose (150 mcg to 600 mcg) in a dose proportional manner, and was about dose-proportional in the dose range of 75 mcg to 150 mcg. Absolute bioavailability of indacaterol after an inhaled dose was on average 43-45%. Systemic exposure results from a composite of pulmonary and intestinal absorption.

Indacaterol serum concentrations increased with repeated once-daily administration. Steady-state was achieved within 12 to 15 days. The mean accumulation ratio of indacaterol, i.e., AUC over the 24-h dosing interval on Day 14 or Day 15 compared to Day 1, was in the range of 2.9 to 3.8 for once-daily inhaled doses between 75 mcg and 600 mcg.

**Distribution:** After intravenous infusion the volume of distribution ( $V_z$ ) of indacaterol was 2,361 L to 2,557 L indicating an extensive distribution. The *in vitro* human serum and plasma protein binding was 94.1 to 95.3% and 95.1 to 96.2%, respectively.

**Biotransformation/Metabolism:** After oral administration of radiolabelled indacaterol in a human ADME (absorption, distribution, metabolism, excretion) study, unchanged indacaterol was the main component in serum, accounting for about one third of total drug-related AUC over 24 h. A hydroxylated derivative was the most prominent metabolite in serum. A phenolic O-glucuronide of indacaterol and hydroxylated indacaterol were further prominent metabolites. A diastereomer of the hydroxylated derivative, a N-glucuronide of indacaterol, and C- and N-dealkylated products were further metabolites identified.

*In vitro* investigations indicated that UGT1A1 is the only UGT isoform that metabolized indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol. *In vitro* investigations further indicated that indacaterol is a low affinity substrate for the efflux pump P-gp.

*In vitro* investigations indicated that indacaterol has negligible potential to cause metabolic interactions with medications (by inhibition or induction of cytochrome P450 enzymes, or induction of UGT1A1) at the systemic exposure levels achieved in clinical practice. *In vitro* investigation furthermore indicated that, *in vivo*, indacaterol is unlikely to significantly inhibit transporter proteins such as P-gp, MRP2, BCRP, the cationic substrate transporters hOCT1 and hOCT2, and the human multidrug and toxin extrusion transporters hMATE1 and hMATE2K, and that indacaterol has negligible potential to induce P-gp or MRP2.

**Excretion:** In clinical studies which included urine collection, the amount of indacaterol excreted unchanged *via* urine was generally lower than 2% of the dose. Renal clearance of indacaterol was, on average, between 0.46 and 1.20 L/h. When compared with the serum clearance of indacaterol of 18.8 L/h to 23.3 L/h, it is evident that renal clearance plays a minor role (about 2 to 6% of systemic clearance) in the elimination of systemically available indacaterol.

In a human ADME study where indacaterol was given orally, the fecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human feces primarily as unchanged parent drug (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose). Mass balance was complete with  $\geq 90\%$  of the dose recovered in the excreta.

Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. The effective half-life, calculated from the

accumulation of indacaterol after repeated dosing ranged from 40 to 56 hours which is consistent with the observed time-to-steady state of approximately 12 to 15 days.

### **Special Populations and Conditions**

A population pharmacokinetic analysis was performed for indacaterol utilizing data from 3 controlled clinical trials that included 1,844 patients with COPD aged 40 to 88 years who received treatment with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>.

The population analysis of the effect of age, gender and weight on systemic exposure in COPD patients after inhalation indicated that ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> can be used safely in all age and weight groups and regardless of gender. It did not suggest any difference between ethnic subgroups in this population. Limited treatment experience is available for the African-American population.

**Hepatic Insufficiency:** Patients with mild and moderate hepatic impairment showed no relevant changes in C<sub>max</sub> or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

**Renal Insufficiency:** Due to the very low contribution of the urinary pathway to total body elimination, a study in renally impaired subjects was not performed.

**Genetic Polymorphism:** The pharmacokinetics of indacaterol was investigated in two different UGT1A1 genotypes – the fully functional [(TA)<sub>6</sub>, (TA)<sub>6</sub>] genotype and the low activity [(TA)<sub>7</sub>, (TA)<sub>7</sub>] genotype (Gilbert's syndrome genotype). The study demonstrated that steady-state AUC and C<sub>max</sub> of indacaterol were 1.2-fold higher in the [(TA)<sub>7</sub>, (TA)<sub>7</sub>] genotype, indicating that systemic exposure to indacaterol is only insignificantly affected by this UGT1A1 genotypic variation.

### **STORAGE AND STABILITY**

Store in a dry place at 25°C; excursions permitted to 15-25°C.  
Protect ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> 75 mcg capsules from light and moisture.  
Keep out of the reach and sight of children.


### **SPECIAL HANDLING INSTRUCTIONS**

- ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> capsules should be used with the ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> inhalation device only. The ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> inhalation device should not be used with any other capsules.
- Capsules should always be stored in the blister and only removed from the blister immediately before use.
- Always use the new ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> inhalation device provided with each new prescription and discard the old device.



## DOSAGE FORMS, COMPOSITION AND PACKAGING

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> hard gelatin capsules for inhalation 75 mcg.

**75 mcg ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> contains:** aluminum blister-packaged 75 mcg indacaterol natural transparent uncolored capsule with black product code “IDL 75” printed above a bar on one side of the capsule and the symbol  printed on the other side, and one ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> inhalation device. Unit Dose (blister pack), Box of 10 or 30 (strips of 10).

Each capsule contains 97 mcg indacaterol maleate equivalent to 75 mcg indacaterol and lactose monohydrate.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

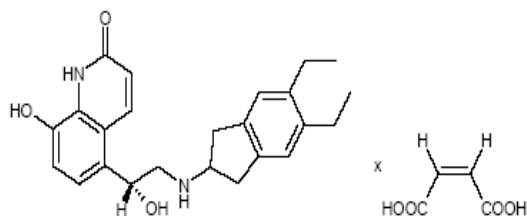
#### Drug Substance

Common name: indacaterol maleate

Chemical name: (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate

Molecular formula and molecular mass:  $C_{24}H_{28}N_2O_3 \cdot C_4H_4O_4$  (508.56)

Structural formula:



Physicochemical properties:

Indacaterol is the pure R-enantiomer of this molecule.

Indacaterol maleate consists of a single polymorphic form, form A.

The pH of indacaterol maleate in 0.1% (g/100 ml) suspension in water at room temperature is 4.9. The pH value of 0.1% (g/100 ml) solution in water/ethanol 80:20 (V/V) at room temperature is 5.0.

The melting range of indacaterol is 195 – 202°C with decomposition.

Indacaterol maleate is a white to very slightly grayish or very slightly yellowish powder. Indacaterol maleate is freely soluble in N-methylpyrrolidone and dimethylformamide, slightly soluble in methanol, ethanol, propylene glycol and polyethylene glycol 400, very slightly soluble in water, isopropyl alcohol and practically insoluble in 0.9% sodium chloride in water, ethyl acetate and n-octanol.

## **Drug Product**

### **ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> 75 mcg inhalation powder hard capsules:**

Each capsule contains 97 mcg indacaterol maleate equivalent to 75 mcg indacaterol. The delivered dose (the dose that leaves the mouthpiece of the ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> device) is 60 mcg indacaterol.

### **ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> INHALATION DEVICE**

The ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> is a plastic inhalation device used for inhaling the content of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> (indacaterol maleate) capsules. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time. Peak inspiratory flow rates (PIFR) achievable through the ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> inhalation device were evaluated in 26 adult patients with COPD of varying severity. Mean PIFR was 95 L/min (range 52-133 L/min) for adult patients. Approximately 95% of the population studied generated a PIFR through the device exceeding 60 L/min.

## CLINICAL TRIALS

The ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> COPD development program included six confirmatory trials that were randomized, double-blinded placebo and active-controlled in design (Trial B2335S, a 26-week seamless adaptive design trial that included an initial 2 week dose-ranging phase; Trials B2354, B2355, and B2346, 12-week trials; Trial B2336, a 26-week trial; and Trial B2334, a 52 week trial). After the initial 2-week dose-ranging portion of the design, Trial B2335S was conducted with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> doses of 150 mcg and 300 mcg once daily, placebo, and an active comparator. Trials B2354 and B2355 were conducted with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> dose of 75 mcg once daily, and placebo. Trial B2346 was conducted with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> dose of 150 mcg once daily and placebo. Trial B2336 was conducted with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> dose of 150 mcg once daily, an active comparator, and placebo.

The efficacy of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> administered at 75 mcg once daily was evaluated in two placebo-controlled clinical trials, Trials B2354 and B2355.

### *Study demographics and trial design*

Trials B2354 and B2355 were 12 week, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies to assess the efficacy and safety of once daily indacaterol (75 mcg o.d.) in patients with COPD. These two trials enrolled 641 patients with a clinical diagnosis of COPD, who were 40 years or older, had a smoking history of at least 10 pack years, had a post-bronchodilator FEV<sub>1</sub> less than 80% and at least 30% of the predicted normal value and a post-bronchodilator ratio of FEV<sub>1</sub> over FVC of less than 70%.

**Table 4 Summary of patient demographics for pivotal clinical trials in COPD**

Study #	Trial design Dosage, route of administration and duration	Study subjects* (n=number)	Mean age (Range)	Gender n (%)
<b>B2354</b>	12 week treatment, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of once daily indacaterol (75 mcg o.d.) in patients with COPD.	Total: n=323 Indacaterol 75 mcg: n=163 Placebo: n=160	64.0 years (40-90)	Male: 176 (54.5) Female: 147 (45.5)
<b>B2355</b>	12 week treatment, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of once daily indacaterol (75 mcg o.d.) in patients with COPD.	Total: n=318 Indacaterol 75 mcg: n=159 Placebo: n=159	61.4 years (40-86)	Male: 172 (54.1) Female: 146 (45.9)

\* Number of patients exposed to treatment or placebo

## Overview of Results

Assessment of efficacy in trials B2354 and B2355 was based on FEV<sub>1</sub>. The primary efficacy endpoint was 24-hour post-dose trough FEV<sub>1</sub> (defined as the average of two FEV<sub>1</sub> measurements taken after 23 hours 10 minutes and 23 hours and 45 minutes after the previous dose) after 12 weeks of treatment. Other efficacy variables included other FEV<sub>1</sub> and FVC time points, rescue medication use, symptoms, transition dyspnoea index (TDI), and health-related quality of life measured using the St. George's Respiratory Questionnaire (SGRQ), a disease-specific patient reported instrument which measures symptoms, activities, and impact of disease on daily life.

## Individual Study Results

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> 75 mcg, showed significantly greater 24-hour post-dose trough FEV<sub>1</sub> compared to placebo at 12 weeks. Results are shown in Table 5.

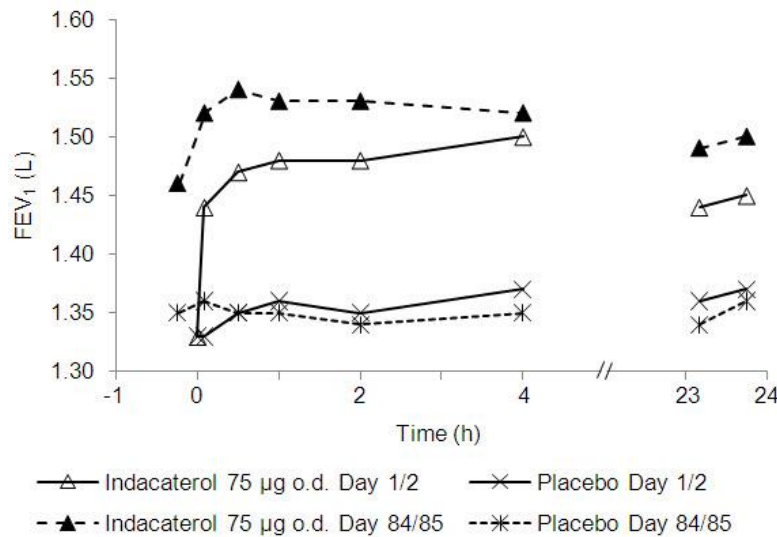
**Table 5** LS Mean for trough FEV<sub>1</sub> at 12 weeks

Treatment	Trough FEV <sub>1</sub> at Week 12 (liters)	Treatment Difference LS Mean (95% CI)
Trial B2354 (N=323)		
Indacaterol 75 mcg	1.38	0.12 (0.08, 0.15)
Placebo	1.26	
Trial B2355 (N=318)		
Indacaterol 75 mcg	1.49	0.14 (0.10, 0.18)
Placebo	1.35	

In addition, serial FEV<sub>1</sub> measurements in patients treated with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> demonstrated a bronchodilatory treatment effect after the first dose compared to placebo at 5 minutes post dose of 0.09 L (Trial B2354) and 0.10 L (Trial B2355). The mean peak improvement relative to baseline within the first 4 hours after the first dose (Day 1) was 0.19 L (Trial B2354) and 0.22 L (Trial B2355) and was 0.24 L (Trial B2354) and 0.27 L (Trial B2355) after 12 weeks. Improvement in lung function observed at week 4 was consistently maintained over the 12-week treatment period in both trials.

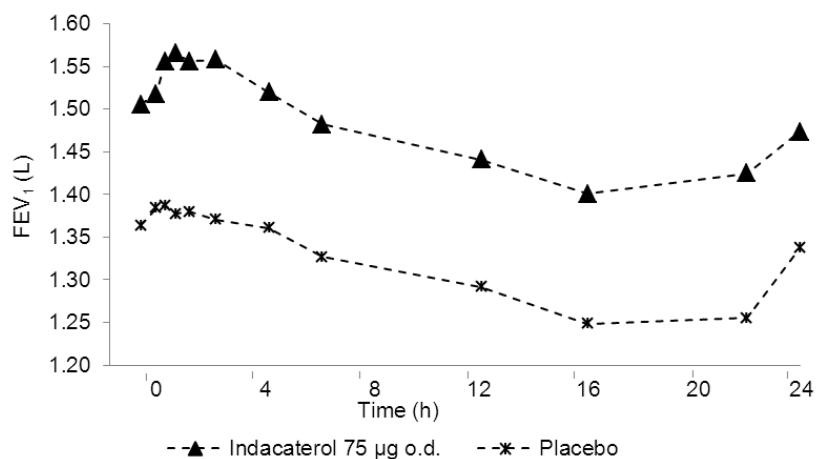
In study B2355, 4-hour serial spirometric measurements were performed in a subset of patients. Serial FEV<sub>1</sub> values over 4 hours at Day 1 and Day 84 and trough FEV<sub>1</sub> values at Day 2 and Day 85 are shown in Figure 1.

**Figure 1** Serial Spirometry Least Square Mean FEV<sub>1</sub> Over 4 Hours at Day 1 and Day 84 and Trough FEV<sub>1</sub> at Day 2 and Day 85



In Trial B2355, 24-hour spirometry was assessed in a subset of 239 patients at week 12. See Figure 2.

**Figure 2** LS Mean FEV<sub>1</sub> time profile curve over 24 hours at Week 12 in Trial B2355



### Symptom Related Outcomes

In the two pivotal clinical trials B2354 and B2355, patients treated with 75 mcg ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> demonstrated an improvement in the TDI focal score, had an increase in the percentage of ‘days able to perform usual daily activities’, and used less daily rescue salbutamol during the trial compared to patients treated with placebo.

At week 12, patients treated with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> 75 mcg demonstrated an improvement over placebo in SGRQ total score of -3.8 with a 95% CI of (-6.2, -1.4) for Study B2354, and -3.6 (95% CI of -6.4, -0.9) for Study B2355.

In conclusion, ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> administered by the BREEZHALER<sup>®</sup> at a dose of 75 mcg once daily provides rapid onset of bronchodilation in patients with stable COPD that was maintained over 24 hours.

Since the bronchodilator effect of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> is still significant 24 hours after inhalation, once-daily maintenance therapy controls bronchoconstriction associated with chronic conditions both during the day and at night.

## **DETAILED PHARMACOLOGY**

### **Animal Pharmacology**

Indacaterol is a potent beta<sub>2</sub> adrenoceptor agonist (EC<sub>50</sub> value of 8.7 nM) with high intrinsic efficacy demonstrated in various in vitro assays, including the recombinant human beta<sub>2</sub> adrenoceptor, the isolated guinea pig trachea, isolated human bronchus and human lung slices. Similarly, high intrinsic activity has been reported in vivo in the guinea pig and the rhesus monkey.

At the recombinant human adrenoceptor expressed in Chinese hamster ovarian cells, indacaterol is a nearly full agonist. The functional selectivity profile of indacaterol over beta<sub>1</sub> human adrenoceptors was similar to that of formoterol, whereas its beta<sub>3</sub> adrenoceptor selectivity profile was similar to that of formoterol and salbutamol.

A fast onset of action was demonstrated for indacaterol in the isolated guinea pig trachea, human bronchus and human lung slices. The potential for once daily dosing was demonstrated in in vitro models by a longer duration of action when compared to salmeterol and formoterol in the electrical field-induced contraction of the isolated guinea pig trachea and human bronchus.

Similarly, a longer duration of action than formoterol and salmeterol was demonstrated in isolated human lung slices contracted with carbachol. In vivo studies have shown 24 hour duration of action against serotonin-induced bronchoconstriction in the guinea pig. The mechanism responsible for the long duration of action of indacaterol has not been unequivocally established. However, it is likely that the mode of action of indacaterol is related to its lipophilicity and its specific interaction with the lipid raft within the cellular membrane.

### **Clinical Pharmacology**

#### **Dose ranging**

Dose selection for ONBREZ BREEZHALER for COPD was based on two placebo-controlled dose-ranging trials (Trial B2356, a 2-week dedicated dose ranging trial with doses of 18.75, 37.5, 75, and 150 mcg once daily and one active comparator, N=552 patients; Trial B2335S, a 26-week adaptive seamless design trial that included an initial 2-week dose ranging phase with doses of 75, 150, 300, and 600 mcg once daily and two active comparators, N=801 patients).

Trial B2356 showed that the effect on FEV<sub>1</sub> in patients treated with ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> 18.75 mcg dose was lower compared to patients treated with other ONBREZ<sup>®</sup>

BREEZHALER<sup>®</sup> doses. Although a dose-response relationship was observed at Day 1, the effect did not clearly differ among the 37.5, 75 and 150 mcg doses by Day 15.

The 2-week dose ranging phase of Trial B2335S included ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> doses of 75, 150, 300, and 600 mcg once daily, placebo, and two active comparators. Although a dose-response relationship was observed at week 2, the effect did not clearly differ among the ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> doses.

Based on the results of the dose-ranging data, a once-daily dose of 75 mcg was selected as it provided clinically relevant bronchodilation.

## **TOXICOLOGY**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

### **Acute Toxicity**

Single oral administrations of indacaterol to rats and mice at doses of 1600 mg/kg were well tolerated. Single oral administrations of indacaterol to dogs at doses between 0.1 and 10 mg/kg were consistent with the pharmacological effect of indacaterol. Higher doses were not tolerated. Single subcutaneous administrations of indacaterol to mice at doses of 5 mg/kg in males and 100 mg/kg in females and to rats at doses up to 100 mg/kg were tolerated without mortalities. Mortality that may be associated with tolerability issues at the administration site was apparent at higher doses.

### **Repeat-dose Toxicity**

The effects of indacaterol seen in toxicity studies in dogs were mainly on the cardiovascular system and consisted of tachycardia and associated increased QTc intervals, arrhythmias and myocardial lesions that included myocardial fibrosis. These are known pharmacological effects and can be explained by the beta<sub>2</sub>-agonistic properties of indacaterol. Beta<sub>2</sub>-agonistic mediated vasodilation and associated hypotension is known to result in a reflex tachycardia, which when excessive is associated with heart lesions. Clinical experience in humans shows that multiple doses at 800 mcg/day or below do not affect heart rate. Other effects noted in repeated-dose toxicity studies were mild irritancy of the upper respiratory tract in rats consisting of rhinitis and epithelial changes of the nasal cavity and larynx. All these findings were observed only at exposures considered sufficiently in excess of the maximum human exposure. The clinical significance of these is likely of little relevance, yet they do remain unclear.



**Table 6 Sub-Chronic and Chronic Toxicology (Pivotal studies)**

Study Type	Species	Route	Doses (Mg/kg/day)	Findings
14-day	Wistar Rat	Inhalation	0, 2.1, 5.8, 17.0	Mild inflammation or irritation of nasal cavity at doses $\geq 5.8$ mg/kg/day. At 17.0 mg/kg/day, exaggerated breathing, increased response to stimuli and increased urinary pH were observed. In addition, accumulation of alveolar macrophages in the lungs was apparent. NOAEL=2.1 mg/kg/day
28-day	Wistar Rat	Inhalation	0, 0.93, 2.77, 8.46	Increased body weight gain, white blood cell parameters and plasma bilirubin were noted at $\geq 0.93$ mg/kg/day. Mild irritation of the nasal cavity was observed at $\geq 2.77$ mg/kg/day (focal, olfactory epithelial degeneration along roof of dorsal meatus) and of the larynx among animals treated at the highest dose (ventral floor at base of epiglottis, focal squamous metaplasia in epithelium lining). All findings were reversible. NOAEL=0.93 mg/kg/day
26-week	Wistar Rat	Inhalation	0.31, 1.02, 3.14	Findings at $\geq 0.31$ mg/kg/day comprised increased skeletal muscle mass, increased body weight and food consumption and decreased blood glucose. At 3.14 mg/kg/day, increased white blood cell counts and mild irritation of the larynx (squamous metaplasia of epithelium of ventral larynx) were observed. Notable decrease in muscle mass following the 4-week recovery period. All other effects were reversible. NOAEL: 1.02 mg/kg/day
14-day	Beagle Dog	Inhalation	0, 0.01, 0.47, 0.93	Reddening of ears and gums, increased heart force and rate, increased breathing rate and decreased blood pressure were apparent at $\geq 0.01$ mg/kg/day. At $\geq 0.47$ mg/kg/day, increased heart rate during ECG evaluations on Day 1 was associated with QTc-prolongation. Cardiac lesions were apparent on completion of treatment at $\geq 0.47$ mg/kg/day (minimal to moderate myocardial necrosis, fibrosis in the papillary muscle). Periportal hepatocellular vacuolation (consistent with increased glycogen concentrations) was seen at all dose levels. NOAEL=0.01 mg/kg/day
28-day	Beagle Dog	Inhalation	0, 0.01, 0.10, 0.97	Reddened gums, salivation and increased heart force were observed at $\geq 0.10$ mg/kg/day. Changes at the highest dose included decreased hemoglobin and hematocrit values and increased QT <sub>c</sub> values during ECG evaluations on day 1 of treatment only. Cardiac lesions (myocardial fibrosis with/without mineralization in left papillary muscle, atrial hemorrhage, pericarditis) were seen at 0.97 mg/kg/day. Myocardial fibrosis was still evident following a 2-week recovery period Periportal vacuolation in the liver was present at $\geq 0.10$ mg/kg/day and was reversible. NOAEL=0.01 mg/kg/day

Study Type	Species	Route	Doses (Mg/kg/day)	Findings
13-week	Beagle Dog	Inhalation	0, 0.02, 0.12, 1.10	Reddening of the ears, gums and abdomen were seen at all doses whilst increased heart rate and force were observed at 1.10 mg/kg/day in week 1 only. Increased body weight gain was noted in males at $\geq 0.12$ mg/kg/day. Increased blood potassium and creatine phosphokinase levels were seen at 1.10 mg/kg/day. Increased heart rate and QT <sub>C</sub> values were apparent at 1.10 mg/kg/day during ECG evaluations on day 1 only. Minimal to moderate cardiac lesions (myocardial fibrosis) were observed in one male and female at the highest dose level. Minimal to mild periportal hepatocellular vacuolation (glycogen-mediated) was seen at all doses NOAEL: 0.12 mg/kg/day
39-week	Beagle Dog	Inhalation	0.03, 0.10, 0.31	Increased body weight gain and blood creatinine levels, were observed at 0.31 mg/kg/day. Slight increases in heart rate and QTc values were also seen at the highest dose during ECG evaluation but excessive tachycardia was not observed. There were no cardiac lesions. Minimal to mild periportal hepatocellular vacuolation was seen at all doses. With the exception of blood creatinine levels, all findings were reversible following a 4-week recovery period. NOAEL: 0.31 mg/kg/day

### Genotoxicity

No evidence of any mutagenic or clastogenic potential was observed for indacaterol.

### Carcinogenicity

The carcinogenic potential of indacaterol has been evaluated in a 2-year inhalation study in rats and a 26-week oral transgenic mouse study. Lifetime treatment of rats resulted in increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in females at doses approximately 136-times the dose of 150 mcg once-daily for humans (on a mg/m<sup>2</sup> basis). Increases in leiomyomas of the rat female genital tract have been similarly demonstrated with other  $\beta_2$ -adrenergic agonist drugs. A 26-week oral (gavage) study in CB6F1/TgrasH2 hemizygous mice with indacaterol did not show any evidence of tumorigenicity at doses approximately 19600-times the dose of 150 mcg once-daily for humans (on a mg/m<sup>2</sup> basis).

**Table 7 Genetic Toxicology and Carcinogenicity**

Study Type	Species	Route	Doses	Findings
Ames test	Salmonella typhimurium strains TA98, TA100, TA1535, TA102, TA97a	<i>In vitro</i>	1.6 to 1000 mcg/plate (in the presence and absence of S9)	Indacaterol was non-mutagenic under the conditions of this assay.

Study Type	Species	Route	Doses	Findings
Chromosome aberration assay	Chinese Hamster cells	<i>In vitro</i>	-S9: 10-32 mcg/mL +S9: 30-171 mcg/mL	Indacaterol was non-clastogenic under the conditions of this assay.
Micronucleus test	Wistar Rat	Subcutaneous	200, 630 and 2000 mg/kg for two days.	Indacaterol had no clastogenic and/or aneugenic potential <i>in vivo</i> under the test conditions used.
Rat carcinogenicity study (2 yr)	Wistar Rat	Inhalation	0, 0, 0.21, 0.62, 2.09 mg/kg/day	Increased muscle mass in males and females and reduced body weight gain in males were observed at all doses. A higher incidence of minimal to mild progressive cardiomyopathy was observed in female animals at 2.09 mg/kg/day. This lesion was also observed at a high incidence in control animals. Increased incidences of ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle were apparent in females at 2.09 mg/kg/day.
Transgenic mouse carcinogenicity study (6 mo)	CB6F1-TgrasH2 mice	PO	0, 100, 300, 600 mg/kg/day	Indacaterol was not carcinogenic in CB6F1-TgrasH2 mice. Tumors were observed in the positive control group receiving N-methyl-N-Nitrosourea (MNU) which confirms the adequacy of the model.

## Reproductive toxicity

Adverse effects with respect to fertility, pregnancy, embryonal/foetal development, pre- and postnatal development could only be demonstrated at doses 390-fold the daily inhalation dose of 150 mcg in humans (on a mg/m<sup>2</sup> basis). The effects, namely an increased incidence of one type of skeletal abnormality, were observed in rabbits. Indacaterol was not teratogenic in rats or rabbits following subcutaneous administration.

**Table 8 Reproductive Toxicology (pivotal studies)**

Study Type	Species	Route	Doses (Mg/kg/day)	Findings
Fertility, reproductive performance and early embryonic development	Wistar Rat	Subcutaneous	0.2, 0.6, 2 bid	Increased body weight parameters and food consumption at ≥0.2 mg/kg/day. Skin lesions at injection sites of animals treated at ≥0.6 mg/kg/day NOEL for effects on fertility, reproductive performance or early embryonic development was 2 mg/kg/day
Embryo-fetal development	Wistar Rat	Subcutaneous	0.1, 0.3 and 1 b.i.d.	Skin lesions at the injection sites at ≥0.1 mg/kg/day. Increased body weight and body weight gain at ≥0.3 mg/kg/day and increased food consumption at 1 mg/kg/day. NOEL for pregnant rat not established NOEL for fetus: 1 mg/kg/day; no teratogenicity

Study Type	Species	Route	Doses (Mg/kg/day)	Findings
Embryo-fetal development	NZW Rabbit	Subcutaneous	0.1, 1, 3	Skin lesions were apparent at the injection sites at 1 and 3 mg/kg/day. At the highest dose, decreased food consumption and an increased incidence of full supernumerary rib were observed. NOEL for pregnant rabbit: 1 mg/kg/day NOEL for fetus: 1 mg/kg/day; no teratogenicity
Peri-postnatal development, reproduction and fertility	Wistar Rat	Subcutaneous	0.1, 0.3 and 1.0	F <sub>0</sub> effects: increased body weight parameters and discoloration at the injection sites at ≥0.3 mg/kg/day. Transient increases in food consumption at 1 mg/kg/day. F <sub>1</sub> effects: decreased body weight parameters at ≥0.3 mg/kg/day. Decrease in number of animals reaching criterion for acquisition/learning in males at 1 mg/kg/day. Fertility and fecundity were affected with a decrease in the number of pregnant animals at 1 mg/kg/day. No effect on mating or other parameters of reproductive performance. NOEL: 0.1 mg/kg/day

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## PART III: CONSUMER INFORMATION

**PrONBREZ® BREEZHALER®**  
Indacaterol maleate

This leaflet is part III of a three-part "Product Monograph" published when ONBREZ® BREEZHALER® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ONBREZ® BREEZHALER®. Contact your doctor or pharmacist if you have any questions about the drug.

Read all of this leaflet carefully before you start taking this medicine. Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or pharmacist. This medicine has been prescribed only for you. Do not give it to anybody else or use it for any other illnesses. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### ABOUT THIS MEDICATION

#### What the medication is used for:

ONBREZ® BREEZHALER® is used to make breathing easier for people who have breathing difficulties due to a lung disease called chronic obstructive pulmonary disease (COPD).

#### What it does:

ONBREZ® BREEZHALER® relaxes the muscles in the walls of the small air passages in the lungs. This helps open up the airways for 24 hours, making it easier for air to get in and out and prevent symptoms, such as wheezing and shortness of breath.

#### When it should not be used:

Do not use ONBREZ® BREEZHALER®:

- To treat asthma
- To treat sudden, severe symptoms of COPD
- If you have a severe allergy to ONBREZ® BREEZHALER® or any of its ingredients. Ask your doctor if you are not sure.
- To treat patients under 18 years of age.

#### What the medicinal ingredient is:

Indacaterol maleate. 75 mcg indacaterol per capsule.

#### What the nonmedicinal ingredients are:

Lactose monohydrate and gelatine (capsule shell).

#### What dosage forms it comes in:

In this pack, you will find a device called an "inhalation device" together with capsules in blister strips.

### WARNINGS AND PRECAUTIONS

#### Serious Warnings and Precautions

ONBREZ® BREEZHALER® should only be used to treat COPD.

You are advised that in patients with asthma, long-acting beta<sub>2</sub>-agonist (LABA) medicines, may increase the chance of death from asthma problems. In a large asthma study, more patients who used another LABA medicine (salmeterol) died from asthma problems compared with patients who did not use that LABA medicine. This finding may also apply to ONBREZ® BREEZHALER®.

**BEFORE you use ONBREZ® BREEZHALER® talk to your doctor or pharmacist if you:**

- have heart problems, such as rapid or irregular heart beat or abnormal electrical signal called "prolongation of the QT interval"
- have high blood pressure
- have epilepsy
- have thyroid gland problems
- have diabetes
- are pregnant or planning to become pregnant. It is not known if ONBREZ® BREEZHALER® may affect your unborn baby.
- are breastfeeding. It is not known if ONBREZ® BREEZHALER® passes into your milk and if it can affect your baby.
- are taking certain medications (see Drug interactions section)

ONBREZ® BREEZHALER® contains lactose (milk sugar) and a small amount of milk proteins. It is possible that allergic reactions may happen in patients who have a severe milk protein allergy.

**During the treatment with ONBREZ® BREEZHALER®, tell your doctor immediately** if you experience any of the following symptoms:

- If you experience a tightness of the chest, coughing, wheezing or breathlessness immediately after inhalation (signs of bronchospasm)
- If you experience difficulties in breathing or swallowing, swelling of tongue, lips and face, hives or itching, skin rash (signs of hypersensitivity reaction). Do not use ONBREZ® BREEZHALER® again before speaking with your doctor.
- If your COPD symptoms (breathlessness, wheezing, cough) do not improve or if they worsen during your treatment

ONBREZ® BREEZHALER® does not relieve sudden symptoms of COPD. Always have a short-acting bronchodilator medicine with you to treat acute symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.

Get emergency medical care if:

- breathing problems worsen quickly
- you use your short-acting bronchodilator medicine, but it does

not relieve your breathing problems

## INTERACTIONS WITH THIS MEDICATION

Tell your doctor or a pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This includes in particular the following medicines:

- medicines used in the treatment of depression or sad mood (e.g. tricyclic antidepressants, monoamine oxidase inhibitors).
- medicines similar to ONBREZ® BREEZHALER® (other LABA) used for your lung disease as it may increase the risk of experiencing possible side effects
- medicines that decrease the level of potassium in your blood. These include diuretics (also known as “water pills” and used to treat hypertension e.g. hydrochlorothiazide), other bronchodilators such as methylxanthines (e.g. theophylline) or steroids (e.g. prednisolone)
- beta-blockers used in the treatment of hypertension or other cardiac problems (e.g. propranolol) or in the treatment of glaucoma (e.g. timolol)

## PROPER USE OF THIS MEDICATION

**Follow your doctor’s instructions carefully. Do not exceed the recommended dose.**

### Usual adult dose

**Inhale the contents of one capsule through the mouth each day,** everyday at the same time, using the ONBREZ® BREEZHALER® inhalation device (see How To Use ONBREZ® BREEZHALER® below), even when you have no breathing problems or other symptoms of COPD.

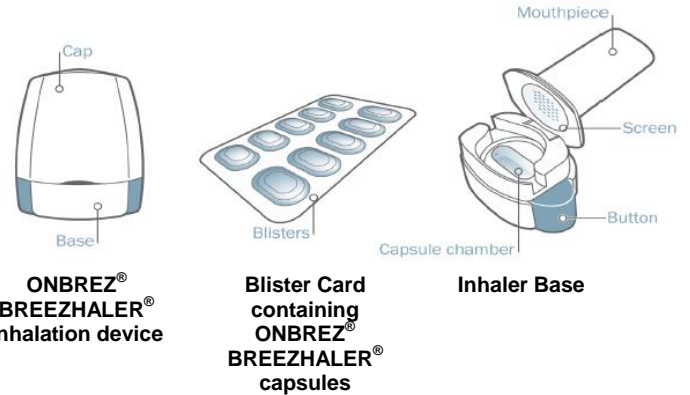
You may inhale this medication in a fasting state or after food or drink.

### *How to inhale ONBREZ® BREEZHALER®:*

Follow the instructions below. You will breathe in (inhale) the medicine in the ONBREZ® BREEZHALER® capsules from the ONBREZ® BREEZHALER® inhalation device. If you have any questions, ask your healthcare provider or pharmacist.

The ONBREZ® BREEZHALER® package contains ONBREZ® BREEZHALER® capsules and one ONBREZ® BREEZHALER® inhalation device.

- The ONBREZ® BREEZHALER® capsules are supplied in one or more blister cards. Each blister card contains 10 transparent capsules.
- The ONBREZ® BREEZHALER® inhalation device consists of a cap and a base.



ONBREZ®  
BREEZHALER®  
Inhalation device

Blister Card  
containing  
ONBREZ®  
BREEZHALER®  
capsules

Inhaler Base

**Your inhalation device is designed to deliver the medicine contained in the capsules. Do not use ONBREZ® BREEZHALER® capsules with any other capsule inhalation device, and do not use the ONBREZ® BREEZHALER® inhalation device to take any other capsule medicine.**

### 1. Pull off the cap



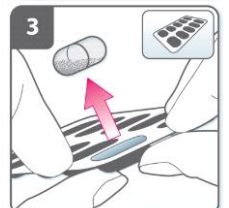
### 2. Open inhalation device:

Hold the base of the ONBREZ® BREEZHALER® inhalation device firmly and tilt the mouthpiece to open the inhalation device.



### 3. Prepare capsule:

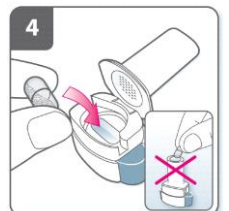
**Immediately before use,** with dry hands, remove one capsule from the blister.



### 4. Insert capsule:

Place the capsule into the capsule chamber.

**Never place a capsule directly into the mouthpiece.**



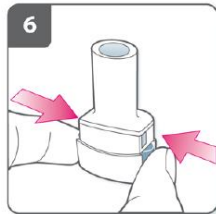
### 5. Close the inhalation device:

Close the inhalation device fully. You should hear a ‘click’ as it fully closes.

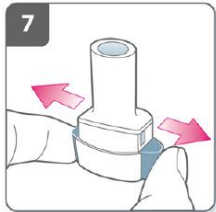


**6. Pierce the capsule:**

Hold the inhalation device upright with the mouthpiece pointing up. Press both buttons fully one time. You should hear a ‘click’ as the capsule is being pierced. **Do not press the piercing buttons more than once.**

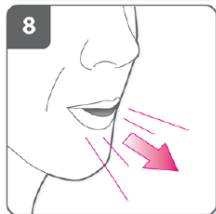


**7. Release the buttons fully.**



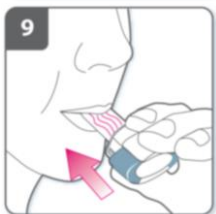
**8. Breathe out:**

Before placing the mouthpiece in your mouth, breathe out fully. **Never blow into the mouthpiece.**



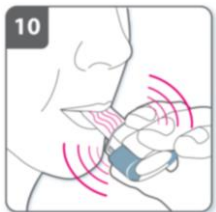
**9. Inhale the medicine:**

Before breathing in, place the mouthpiece in your mouth and close your lips firmly around the mouthpiece. Hold the inhalation device with the buttons to the left and right (not up and down). Breathe in rapidly but steadily, as deeply as you can. **Do not press the piercing buttons.**



**10. Note:**

As you breathe in through the inhalation device, the capsule spins around in the chamber and you should hear a whirring noise. You will experience a sweet taste as the medicine goes into your lungs. If you do not hear a whirring noise, the capsule may be stuck in the capsule cavity. If this occurs, open the inhalation device and carefully loosen the capsule by tapping the base of the device. **Do not press the piercing buttons to loosen the capsule.** Repeat steps 8 and 9 if necessary.



**11. Hold breath:**

**Continue to hold your breath** for at least 5-10 seconds or as long as comfortably possible while removing the inhalation device from your mouth. Then breathe out.



Open the inhalation device to see if any powder is left in the capsule. If there is powder left in the capsule, close the inhalation device and repeat steps 8 to 11. Most people are able to empty the capsule with one or two inhalations. Some people occasionally cough soon after inhaling the medicine. If you do, don't worry, as long as the capsule is

empty, you have received the full dose.

**12. Remove capsule:**

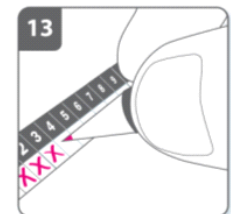
After you have finished taking your daily dose of ONBREZ® BREEZHALER®, open the mouthpiece again, remove the empty capsule by tipping it out, and discard it. Close the inhalation device and replace the cap.



**Do not store the capsules in the ONBREZ® BREEZHALER® inhalation device.**

**13. Mark daily dose tracker:**

On the inside of the pack there is a daily dose tracker. Put a mark in today's box if it helps to remind you of when your next dose is due.



**Additional Information**

Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed or inhaled. The chances of the capsule shattering will be increased if the capsule is pierced more than once (Step 6).

**Remember:**

- **Do not swallow ONBREZ® BREEZHALER® capsules**
- **Only use the ONBREZ® BREEZHALER® inhalation device contained in this pack**
- **ONBREZ® BREEZHALER® capsules must always be stored in the blister, and only removed immediately before use**
- **Never place an ONBREZ® BREEZHALER® capsule directly into the mouthpiece of the ONBREZ® BREEZHALER® inhalation device**
- **Do not press the piercing buttons more than once**
- **Never blow into the mouthpiece of the ONBREZ® BREEZHALER® inhalation device**
- **Always release the push buttons before inhalation**
- **Never wash the ONBREZ® BREEZHALER® inhalation device with water. Keep it dry.**
- **Never take the ONBREZ® BREEZHALER® inhalation device apart**
- **Always use the new ONBREZ® BREEZHALER® inhalation device that comes with your new ONBREZ® BREEZHALER® medication pack (use a new ONBREZ® BREEZHALER® inhalation device each month)**
- **Do not store the capsules in the ONBREZ® BREEZHALER® inhalation device**
- **Always keep the ONBREZ® BREEZHALER® inhalation device and ONBREZ® BREEZHALER® capsules in a dry place**

**Overdose:**

If you have accidentally inhaled too much ONBREZ® BREEZHALER® or if someone else accidentally inhaled your medicine, contact a doctor or hospital for advice immediately.



Show the pack of ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>. Medical attention may be needed.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**

If you forget a dose, inhale the next dose on the usual time the next day. Do not take a double dose to make up for a forgotten dose.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like all medicines, ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> can cause side effects in some people.

Some people occasionally cough soon after inhaling the medicine. If you do, don't worry, as long as the capsule is empty, you have received the full dose.

Common side effects include:

- Nausea
- Upper respiratory tract infections
- Muscle cramp
- Headache
- Cough
- Irritation of the mouth or throat

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediately emergency medical attention
		Only if severe	In all cases	
Uncommon	Bronchospasm with wheezing or coughing and difficulty in breathing			✓
	Muscle weakness, muscle spasms, or an abnormal heart rhythm (low blood potassium level)			✓

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediately emergency medical attention
		Only if severe	In all cases	
	Allergic reaction: fainting (low blood pressure), rash, hives or itching, swelling of the tongue, lips and face or difficulty in swallowing			✓
Unknown	Fast or irregular heartbeat	✓		

*This is not a complete list of side effects. For any unexpected effects while taking ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup>, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Store ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> at room temperature between 15 to 25°C. Protect ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> 75 mcg capsules from light and moisture. Do not use after the expiry date shown on the box.

ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> capsules must always be stored in the blister, and only removed immediately before use.

Keep ONBREZ<sup>®</sup> BREEZHALER<sup>®</sup> and all medicines out of the sight and reach of children.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, Ontario  
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the product monograph, prepared for health professionals can be found at: <http://www.novartis.ca>

or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at: 1-800-363-8883

This leaflet was prepared by:  
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Last revised: January 2, 2015

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